

Reaction-diffusion waves of blood coagulation[☆]

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Abstract

One of the main characteristics of blood coagulation is the speed of clot growth. This parameter strongly depends on the speed of propagation of the thrombin concentration in blood plasma. In the current work we consider a mathematical model of the coagulation cascade and study existence, stability and speed of propagation of the reaction-diffusion waves of blood coagulation. We also develop a simplified one-equation model that reflects the main features of the thrombin wave propagation. For this equation we estimate the wave speed analytically. The resulting formulas provide a good approximation for the speed of wave propagation in a more complex model as well as for the experimental data.

Keywords: blood coagulation, reaction-diffusion wave, speed of propagation

2000 MSC: 35C07, 92C45, 35K57

[☆]The last author was supported by the grant of Russian Science Foundation, project no.15-11-00029 and by the program PICS CNRS 6583 Matbio.

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1. Introduction

The main function of the coagulation system is terminating bleeding, caused by the vessel wall damage by covering the injury site with a fibrin clot. The reaction of fibrin polymerization appears at the final stage of the proteolytic enzymatic cascade where the activated clotting factors act as catalysts for activation of the others [1, 2]. Mature form of fibrin molecules can aggregate into long branching fibers and form a complex network which serves as a thrombus scaffold. The key enzyme of the coagulation cascade is thrombin as it catalyzes fibrinogen conversion to fibrin and distribution of the thrombin concentration has a crucial influence on the kinetics of the clot formation [3, 4, 1]. To prevent the spontaneous formation of thrombi the activation reactions are regulated by the action of plasma inhibitors [5, 6, 7, 8]. The balance between coagulation and anti-coagulation systems is important for the normal organism functioning and any alternations can lead to the severe pathological states: thrombosis or, on the contrary, disseminative bleeding [9, 10].

The key enzyme of the coagulation cascade is thrombin since it catalyzes fibrinogen cleavage to fibrin which in turn forms hemostatic clot. Formation of thrombin appears due to the prothrombin activation in the coagulation cascade. The process can be launched by the tissue factor expressed to the blood flow in case of the endothelium rupture (extrinsic pathway), or through the activation of factor XII which triggers activation of factor XI in case of the contact with the foreign surface (contact activation) [2, 11, 12]. Both pathways lead to the activation of factor X that contributes to the prothrombin conversion to thrombin [2]. Once the thrombin concentration reaches the threshold value, further prothrombin activation takes place due to the positive feedback loops of the coagulation cascade (intrinsic pathway) [11, 2, 13]. Thrombin controls activation of factor XI [12] and also of factors V [7] and VIII whose activated forms (Va, VIIIa) increase catalytic activity of factors Xa and IXa by formation of the prothrombinase and intrinsic kinase complexes respectively [14, 2, 15, 16] (Fig. 1).

Influence of different factors on the coagulation process was studied both experimentally and using theoretical approaches. As compared to the experiment, parameters in theoretical studies can be varied much easier allowing to detect not only experimentally observed regimes of blood coagulation [17, 18, 19, 20, 21] but also to suppose their possible variations for the conditions that are hard to reproduce in the experiment [22]. Model results

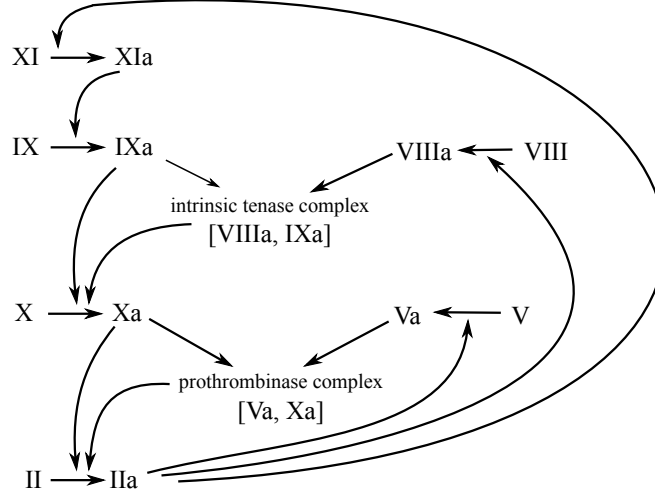


Figure 1: The main activation reactions of the intrinsic pathway of the coagulation cascade. Thrombin (IIa) catalyzes activation of factors V, VIII, XI; factors XIa and IXa catalyze activation of factors IX and X respectively; factors VIIIa and Va form active complexes with factors IXa and Xa respectively and further increase thrombin production.

also provide data about the possible spatiotemporal distribution of all the blood factors participating in the coagulation cascade, while the main parameter used to measure the dynamics of the clot growth experimentally is fibrin clot density [20, 19, 23, 13, 24].

One of the main criteria used for the validation of the computational models of coagulation system is the spatio-temporal distribution of the thrombin concentration. During the amplification phase of the blood coagulation process, thrombin concentration propagates in the direction from the injury site to the vascular lumen. According to the experimental data, after thrombin concentration exceeds some threshold value, the speed of the clot growth does not anymore depend on the way of the initial activation of the coagulation system [11, 24] and thrombin wave profile stays constant in time [14, 20, 25, 26]. In terms of mathematical models, such behavior corresponds to the traveling wave solutions of the system of partial differential equations on the reactions of the coagulation cascade [19, 25, 26, 27, 22, 28].

Despite numerous evidence of the wave behavior of the thrombin concentration profile, theoretical analysis of the observed phenomena is lacking in previous model studies of blood coagulation. That is why in our work we focus on the detailed theoretical investigation of the mathematical model

of the intrinsic pathway of the coagulation system (Section 2). We derive conditions on the existence and stability of the traveling wave solutions corresponding to the amplification phase of coagulation cascade (Section 3) and demonstrate an important property of their speed of propagation (Section 4).

We also pay particular attention to the calculation of the speed of thrombin propagation. Serving as an important indicator of blood coagulation disorders [9, 10], the speed of thrombin propagation in mathematical models is usually measured according to the results of the computational simulations [25, 28, 29] or using the combination of analytical and numerical approaches as it was done by [27]. In Section 5 of the current work we propose an alternative approach and derive theoretical estimates for the speed of the thrombin wave propagation by the reduction of the initial system to one equation on thrombin concentration. We compare the estimates given by analytical formulas with computational values of the speed as well as with the experimental data.

2. Mathematical model

We consider the following model of the intrinsic pathway of blood coagulation:

$$\begin{aligned}
\frac{\partial T}{\partial t} &= D\Delta T + \left(k_2 U_{10} + \overline{k_2} \frac{k_{510}}{h_{510}} U_{10} U_5 \right) \left(1 - \frac{T}{T_0} \right) - h_2 T, \\
\frac{\partial U_5}{\partial t} &= D\Delta U_5 + k_5 T - h_5 U_5, \\
\frac{\partial U_8}{\partial t} &= D\Delta U_8 + k_8 T - h_8 U_8, \\
\frac{\partial U_9}{\partial t} &= D\Delta U_9 + k_9 U_{11} - h_9 U_9, \\
\frac{\partial U_{10}}{\partial t} &= D\Delta U_{10} + k_{10} U_9 + \overline{k_{10}} \frac{k_{89}}{h_{89}} U_9 U_8 - h_{10} U_{10}, \\
\frac{\partial U_{11}}{\partial t} &= D\Delta U_{11} + k_{11} T - h_{11} U_{11}.
\end{aligned} \tag{1}$$

Here, T , U_i denote the concentrations of thrombin and activated forms of the i -th factor respectively, T_0 denotes the initial prothrombin concentration. First term of each equation corresponds to the diffusion of the factors in blood plasma while other terms describe chemical reactions of the coagulation cascade. $k_i, \overline{k_i}$ denote the rates of activation reactions and h_i denote

inhibition of the activated factors. k_{ij} and h_{ij} denote the rates of formation and inhibition respectively for the intrinsic kinase and prothrombinase complexes. Corresponding equation terms have the given form due to the assumption of the fast reactions of the complex formation.

In the current study we focus on the propagation stage of the coagulation cascade and thus suppose the initial amount of activated factors to be formed in the proximity of the vessel wall. Therefore we use step functions of thrombin and activated factor concentrations as initial conditions for the simulation. In order to take into account the activation of factor XI by factor XIIa we take constant influx boundary condition on the left side of the domain and zero-flux boundary conditions on the right side.

The similar model has previously demonstrated a good agreement with experimental data [30, 28]. The main assumption of the model concerns taking inactivated factor concentrations to be constant. Numerical computations showed that concentrations of the precursors of active factors do not significantly change during the simulation [28]. Therefore, depletion of the precursors can be ignored. The only precursor whose concentration was considered as variable in the model of [30] is prothrombin. Thus, the first equation of our model replaces two following equations considered in [30, 28]:

$$\frac{\partial T}{\partial t} = D\Delta T + k_2 U_{10} \frac{\bar{T}}{\bar{T} + K_{2m}} + \bar{k}_2 \frac{k_{510}}{h_{510}} U_{10} U_5 \frac{\bar{T}}{\bar{T} + K_{2m}} - h_2 T, \quad (2)$$

$$\frac{\partial \bar{T}}{\partial t} = D\Delta \bar{T} - k_2 U_{10} \frac{\bar{T}}{\bar{T} + K_{2m}} - \bar{k}_2 \frac{k_{510}}{h_{510}} U_{10} U_5 \frac{\bar{T}}{\bar{T} + K_{2m}}, \quad (3)$$

with \bar{T} denoting prothrombin concentration. For $h_2 = 0$ both models coincide, and for low values of h_2 they would be very close. For the physiological values of thrombin inhibition, in the model of [28] we observe propagation of non-monotone thrombin wave while system (1) gives monotone traveling waves with higher value of maximal concentration (Fig. 2). Despite this difference, the speed of thrombin wave propagation appears to be very close for both models (Fig. 2) and thus further we use system (1) as an approximation of the thrombin propagation process.

3. Existence and stability of the traveling wave solutions

Let us set $u = (T, U_5, U_8, U_9, U_{10}, U_{11})$. Then system (1) can be written in the vector form:

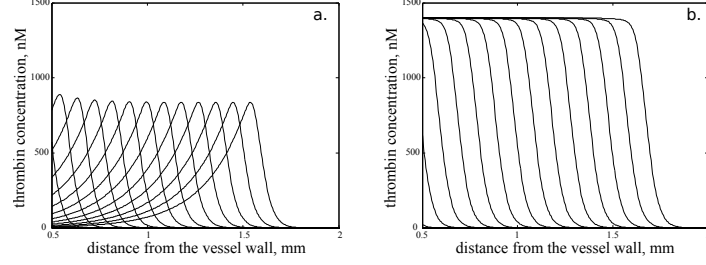


Figure 2: Propagation of thrombin wave for the model of [28] (a) and for the reduced model (1) (b). Concentration profiles are plotted every 2 min of physical time, the speed of the wave propagation is about 0.05 mm/min. Parameters of the simulations are provided in Tab. C.1.

$$\frac{\partial u}{\partial t} = D\Delta u + F(u), \quad (4)$$

where $F = (F_1, \dots, F_6)$ is the vector of reaction rates in equations (1). It satisfies the following property:

$$\frac{\partial F_i}{\partial u_j} \geq 0, \quad \forall i \neq j.$$

This class of systems is called monotone systems and has a number of properties similar to those for one scalar equation including the maximum principle. It allows the proof of existence and stability of the wave solutions for monotone systems as well as the estimation of the wave propagation speed [31]. In order to apply these results to the considered system describing intrinsic pathway functioning we start with the analysis of the existence and stability of the stationary points of system (1).

3.1. Stationary points of the kinetic system

Consider the system of ordinary differential equations:

$$\frac{du}{dt} = F(u). \quad (5)$$

Its equilibrium points satisfy the following relations:

$$U_5 = \frac{k_5}{h_5}T, \quad U_8 = \frac{k_8}{h_8}T, \quad U_{11} = \frac{k_{11}}{h_{11}}T, \quad U_9 = \frac{k_9 k_{11}}{h_9 h_{11}}T, \quad (6)$$

$$U_{10} = \frac{k_9 k_{11}}{h_{10} h_9 h_{11}} \left(k_{10}T + \overline{k_{10}} \frac{k_{89}}{h_{89}} T^2 \right), \quad (7)$$

where T is a solution of the equation $P(T) = 0$. Here $P(T) = aT^4 + bT^3 + cT^2 + dT$,

$$\begin{aligned} a &= \frac{\overline{k_{10}} k_{89} k_8 \overline{k_2} k_5 k_{510} k_9 k_{11}}{h_{89} h_8 h_5 h_{10} h_{510} h_9 h_{11}}, & d &= -\frac{k_2 k_{10} k_9 k_{11}}{h_9 h_{11} h_{10}} + h_2 T_0, \\ b &= -\frac{\overline{k_{10}} k_{89} k_8 \overline{k_2} k_5 k_{510} k_9 k_{11}}{h_{89} h_8 h_5 h_{10} h_{510} h_9 h_{11}} T_0 + \frac{k_{10} \overline{k_2} k_5 k_{510} k_9 k_{11}}{h_5 h_{10} h_{510} h_9 h_{11}} + \frac{\overline{k_2} k_{10} k_{89} k_8 k_9 k_{11}}{h_{89} h_8 h_9 h_{11}}, \\ c &= -\frac{k_{10} \overline{k_2} k_5 k_{510} k_9 k_{11}}{h_5 h_{10} h_{510} h_9 h_{11}} T_0 + \frac{k_2 k_{10} k_9 k_{11}}{h_9 h_{11}} - \frac{k_2 k_{89} k_8 k_9 k_{11}}{h_{89} h_8 h_9 h_{11} h_{10}} T_0. \end{aligned}$$

Hence, the stationary points of system (5) can be found through the stationary points T^* of the equation

$$\frac{dT}{dt} = -P(T), \quad (8)$$

and equalities (6), (7).

Let us determine the number of positive roots of the polynomial $P(T)$. We set $P(T) = TQ(T)$, where $Q(T) = aT^3 + bT^2 + cT + d$. The number of positive roots of $Q(T)$ can be found as follows. First, we consider a function $Q'(T) = 3aT^2 + 2bT + c$. If it has no zeros, then $Q(T)$ is increasing and has one positive root if and only if $Q(0) < 0$. Otherwise, we denote by T_1, T_2 the nonzero solutions of the equation $Q'(T) = 0$: $T_{1,2} = (-b \pm \sqrt{b^2 - 3ac})/(3a)$. Then, the polynomial $Q(u)$ has one positive root in one of the cases:

- $T_1 \leq 0, Q(0) < 0$,
- $0 \leq T_1 < T_2, Q(0) < 0$ and $Q(T_1) > 0, Q(T_2) > 0$ or $Q(T_1) < 0$

and it has two positive roots if $0 < T_2, Q(0) > 0, Q(T_2) < 0$.

Stability of the stationary points of system (5) can be determined from the stability of stationary points of equation (8). The following theorem holds (see Appendix A for the proof).

140 **Theorem 1.** *There is one to one correspondence between stationary solutions*
141 *$u^* = (T^*, U_5^*, U_8^*, U_9^*, U_{10}^*, U_{11}^*)$ of system (1) and the stationary points T^* of*
142 *equation (8) given by (6), (7). The principal eigenvalue of the matrix $F'(u^*)$*
143 *is positive (negative) if and only if $P'(T^*) < 0$ ($P'(T^*) > 0$).*

144 Thus, we can make the following conclusions about the existence and
145 stability of stationary points of the kinetic system of equation (5). It always
146 has a trivial solution $u^* = 0$. It has one (two) positive solution if and only if
147 the polynomial $P(T)$ has one (two) positive root(s). A positive solution u^*
148 is stable if and only if $P'(T^*) > 0$.

149 3.2. Wave existence and stability

150 We can now formulate a theorem on the existence of wave solutions in
151 system (1).

152 **Theorem 2.** *Suppose that $P(T^*) = 0$ for some $T^* > 0$ and $P'(0) \neq$
153 0 , $P'(T^*) \neq 0$. Let $u^* = (T^*, U_5^*, U_8^*, U_9^*, U_{10}^*, U_{11}^*)$ be the corresponding
154 stationary solutions of system (5) determined by relations (6), (7).*

- 155 • *Monostable case. If there are no other positive roots of the polynomial*
156 *$P(T)$, then system (1) has monotonically decreasing traveling wave so-*
157 *lutions $u(x, t) = w(x - ct)$ with the limits $u(+\infty) = 0, u(-\infty) = u^*$ for*
158 *all values of the speed c greater than or equal to the minimal speed c_0 ,*
- 159 • *Bistable case. If there is one more positive root of the polynomial $P(T)$*
160 *in the interval $0 < T < T^*$, then system (1) has a monotonically*
161 *decreasing traveling wave solutions $u(x, t) = w(x - ct)$ with the limits*
162 *$u(+\infty) = 0, u(-\infty) = u^*$ for a unique value of c .*

163 The proof of Theorem 2 follows from the general results on the existence
164 of waves for monotone systems of equation [31, 32]. Let us note that the
165 conditions on the stability of stationary points follow from the assumption
166 of Theorem 2 and Theorem 1. We have $P'(T^*) > 0$ in both cases since it is
167 the largest root of the polynomial increasing at infinity. The sign of $P'(0)$
168 is negative if there is no other root of $P(T)$ in between of 0 and T^* and the
169 sign is positive if $P(T)$ has one more root.

170 Monotone traveling wave solutions of monotone systems are asymptoti-
171 cally stable [31, 32] that gives global stability in the bistable case. In the
172 monostable case the wave is globally stable for the minimal speed c_0 and
173 stable with respect to small perturbations in a weighted norm for $c > c_0$ [32].

174 The unique wave speed in the bistable case and the minimal wave speed
175 in the monostable case admit minimax representations. Below we use such
176 representations for the bistable system since this case is more appropriate
177 for the applications considered in the current work. Indeed, traveling wave
178 solution of system (1) describes propagation of the thrombin concentration
179 in blood plasma due to the reactions of the coagulation cascade. In this
180 system the convergence to the traveling wave solution takes place only if the
181 initial concentrations of blood factors exceed some critical level, otherwise the
182 clot formation does not start because of the action of plasma inhibitors. This
183 dependency on the initial conditions and stability of zero solution correspond
184 to the bistable case. In the monostable case, on the contrary, any small
185 perturbation would result in the solution converging to the propagating wave.
186 In terms of the coagulation system functioning, monostable case corresponds
187 to the spontaneous disseminated coagulation blocking blood circulation.

188 Finally, let us note that in Theorem 2 we consider only the case of a
189 single positive root of the polynomial and the case of two positive roots. If
190 $P(T)$ has three positive roots the system would be monostable with a stable
191 intermediate stationary point. While this case is interesting from the point
192 of view of wave existence and stability, it is less relevant for the modeling of
193 blood coagulation, and we will not discuss it here.

194 4. Speed of wave propagation

195 One of the main objectives of this work is to obtain an analytical approx-
196 imation of the wave speed for the blood coagulation model (1). We proceed
197 in two steps. First, we reduce system (1) to a single equation and justify
198 this reduction. Then, we obtain some estimates of the wave speed for one
199 reaction-diffusion equation.

200 4.1. System reduction

201 In order to simplify the presentation, we describe the method of reduction
202 for the system of two equations:

$$u'' + cu' + f(u, v) = 0, \tag{9}$$

$$v'' + cv' + \frac{1}{\varepsilon}(au - bv) = 0, \tag{10}$$

203 where ε is a small parameter, $\frac{\partial f}{\partial v} > 0$ and system (9)–(10) is bistable. If we
 204 multiply the second equation by ε and take a formal limit as $\varepsilon \rightarrow 0$, then we
 205 have $v = \frac{a}{b}u$, and the first equation can be rewritten as follows:

$$u'' + cu' + f\left(u, \frac{a}{b}u\right) = 0. \quad (11)$$

206 Let us recall that the value of the speed $c = c_\varepsilon$ in system (9)–(10) and $c = c_0$
 207 for the scalar equation (11) are unknown, and in general they are different
 208 from each other. We will demonstrate that $c_\varepsilon \rightarrow c_0$ as $\varepsilon \rightarrow 0$:

209 **Theorem 3.** *The speed of wave propagation for system (9)–(10) converges*
 210 *to the speed of the wave propagation for equation (11) as $\varepsilon \rightarrow 0$.*

211 Singular perturbations of traveling waves are extensively studied by [31].
 212 Here we present another method of proof based on the estimates of the wave
 213 speed. This method is simpler and gives not only the limiting value of the
 214 speed for $\varepsilon = 0$ but also the estimates of the speed value for any positive ε .
 215 In the following sections we describe the approach in details and construct
 216 the wave speed estimates for system (9)–(10).

217 4.2. Wave speed estimate

218 We get the following estimates from the minimax representation of the
 219 wave speed in the bistable case [32] :

$$\min\left(\inf_x S_1(\rho), \inf_x S_2(\rho)\right) \leq c \leq \max\left(\sup_x S_1(\rho), \sup_x S_2(\rho)\right), \quad (12)$$

220 where

$$S_1(\rho) = \frac{\rho_1'' + f(\rho_1, \rho_2)}{-\rho_1'}, \quad S_2(\rho) = \frac{\rho_2'' + (a\rho_1 - b\rho_2)/\varepsilon}{-\rho_2'},$$

221 $\rho = (\rho_1, \rho_2)$ is an arbitrary test function continuous together with its second
 222 derivatives, monotonically decreasing (component-wise) and having the same
 223 limits at infinity as the wave solution, $\rho(+\infty) = 0$, $\rho(-\infty) = u^*$.

224 Let us choose the following test functions:

$$\rho_1 = u_0, \quad \rho_2 = \frac{a}{b}u_0 - \varepsilon f\left(u_0, \frac{a}{b}u_0\right) \frac{a}{b^2}, \quad (13)$$

225 where u_0 is the solution of (11). Neglecting the second-order terms with
 226 respect to ε , we get:

$$\begin{aligned} S_1(\rho) &= \left(u_0'' + f\left(u_0, \frac{a}{b}u_0 - \varepsilon \frac{a}{b^2}f\left(u_0, \frac{a}{b}u_0\right)\right) \right) / (-u_0') = \\ &= \left(u_0'' + f\left(u_0, \frac{a}{b}u_0\right) - \varepsilon \frac{a}{b^2}f_v\left(u_0, \frac{a}{b}u_0\right)f\left(u_0, \frac{a}{b}u_0\right) \right) / (-u_0') = c_0 + \varepsilon\varphi(x), \end{aligned} \quad (14)$$

227 where

$$\varphi(x) = \frac{a}{b^2 u_0'} f_v\left(u_0, \frac{a}{b}u_0\right) f\left(u_0, \frac{a}{b}u_0\right),$$

228 and c_0 is the value of the speed in (11). Next,

$$S_2(\rho) = \frac{u_0'' + f\left(u_0, \frac{a}{b}u_0\right) - \frac{\varepsilon}{b}\left(f\left(u_0, \frac{a}{b}u_0\right)\right)''}{-u_0' + \frac{\varepsilon}{b}\left(f\left(u_0, \frac{a}{b}u_0\right)\right)'} = c_0 + \varepsilon\psi(x), \quad (15)$$

229 where

$$\psi = \frac{c_0}{b u_0'} \left(f\left(u_0, \frac{a}{b}u_0\right)\right)' + \frac{1}{b u_0'} \left(f\left(u_0, \frac{a}{b}u_0\right)\right)''.$$

230 Hence, from (14), (15) we obtain the estimate

$$c_0 + \varepsilon \max \left\{ \min_x \varphi, \min_x \psi \right\} \leq c \leq c_0 + \varepsilon \min \left\{ \max_x \varphi, \max_x \psi \right\}, \quad (16)$$

231 where c_0 is the wave propagation speed for (11), the functions $\varphi(x)$, $\psi(x)$
 232 are bounded. The proof of Theorem 3 follows from this estimate.

233 5. One equation model

234 5.1. Reduction to the equation on thrombin concentration

235 If the reaction rate constants in the equations of system (1) for the vari-
 236 ables U_9 , U_{10} , U_5 and U_8 are sufficiently large, then we can replace these
 237 equations by the following algebraic relations (Section 4.1):

$$U_5 = \frac{k_5}{h_5}T, \quad U_8 = \frac{k_8}{h_8}T, \quad U_9 = \frac{k_9}{h_9}U_{11}, \quad U_{10} = U_{11} \frac{k_9}{h_9 h_{10}} \left(k_{10} + \frac{\overline{k_{10}} k_{89}}{h_{89}} \frac{k_8}{h_8} T \right).$$

238 Then, instead of system (1) we obtain the following system of two equations:

$$\begin{aligned} \frac{\partial T}{\partial t} &= D\Delta T + U_{11} \frac{k_9}{h_9 h_{10}} \left(k_{10} + \frac{\overline{k_{10}} k_{89}}{h_{89}} \frac{k_8}{h_8} T \right) \left(k_2 + \frac{\overline{k_2} k_{510}}{h_{510}} \frac{k_5}{h_5} T \right) \left(1 - \frac{T}{T_0} \right) - h_2 T, \\ \frac{\partial U_{11}}{\partial t} &= D\Delta U_{11} + k_{11} T - h_{11} U_{11}. \end{aligned} \quad (17)$$

239 Similarly, we can reduce this system to the single equation:

$$\frac{\partial T}{\partial t} = D\Delta T + \frac{k_9 k_{11}}{h_9 h_{10} h_{11}} T \left(k_{10} + \frac{\overline{k_{10}} k_{89}}{h_{89}} \frac{k_8}{h_8} T \right) \left(k_2 + \frac{\overline{k_2} k_{510}}{h_{510}} \frac{k_5}{h_5} T \right) \left(1 - \frac{T}{T_0} \right) - h_2 T. \quad (18)$$

240 We realize this reduction in two steps in order to compare the one-equation
 241 model to system (1) as well as to the intermediate model of two equa-
 242 tions (17). Numerical simulations show that for the values of parameters
 243 in the physiological range [33, 25], all three models give the wave speed of
 244 the same order of magnitude (Fig. 3). The two equation model (17) gives a
 245 better approximation of model (1) than the single equation (18). However,
 246 the latter demonstrates the same parameter dependence of the wave speed
 247 as other models. Taking into account the complexity of the initial model (1),
 248 the approximation provided by one equation is acceptable. Below we obtain
 249 the analytical formulas for the wave speed for the one equation model.

250 5.2. Dimensionless model

251 In dimensionless variables

$$T = T_0 u, \quad t = \frac{\tilde{t}}{h_2}, \quad D = \tilde{D} h_2, \quad (19)$$

252 we rewrite equation (18) in the following form:

$$\frac{\partial u}{\partial \tilde{t}} = \tilde{D} \Delta u + M_1 u (1 + M_2 u) (1 + M_3 u) (1 - u) - u, \quad (20)$$

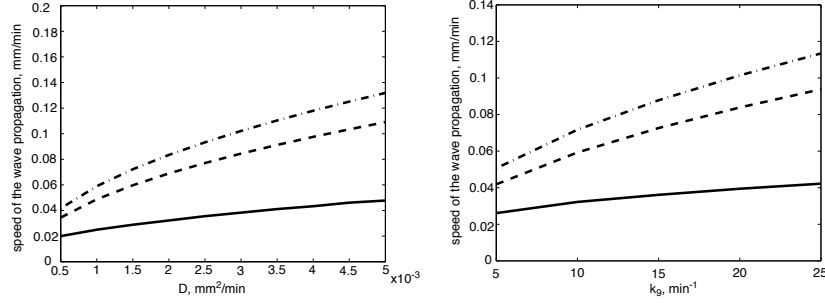


Figure 3: Speed of wave propagation (mm/min) as a function of D (left) and k_9 (right). Solid line: reduced model (1); dashed line: two-equation model (17); dash-dot line: one equation model (18). Parameters of the simulations are provided in Tab. C.1.

where:

$$M_1 = \frac{k_2 k_9 k_{10} k_{11}}{h_2 h_9 h_{10}}, \quad M_2 = \frac{k_8 k_{89} \overline{k_{10}}}{k_{10} h_8 h_{89}} T_0, \quad M_3 = \frac{\overline{k_2} k_5 k_{510}}{k_2 h_5 h_{510}} T_0.$$

253 Analysis of the rate constant values allows us to further simplify the equation.
 254 As $M_3 \gg 1$ we can approximate equation (20) by the following equation:

$$\frac{\partial u}{\partial \tilde{t}} = \tilde{D} \Delta u + M_1 M_3 u^2 (1 + M_2 u) (1 - u) - u. \quad (21)$$

255 Let us note that the first component of the term $u_1^2(1 + M_2 u_1)$ corresponds to
 256 the prothrombin activation by the factor Xa and the second one corresponds
 257 to the prothrombin activation by the [Va, Xa] complex. Since during the
 258 propagation phase the rate of activation by prothrombinase complex is several
 259 orders of magnitude higher than the activation by Xa itself [33], we can
 260 neglect the first component. Thus, applying the assumption of the detailed
 261 equilibrium for the second equation, we finally obtain the following equation
 262 for the thrombin concentration:

$$\frac{\partial u_1}{\partial \tilde{t}} = \tilde{D} \Delta u_1 + b u_1^3 (1 - u_1) - u_1, \quad (22)$$

263 where:

$$b = M_1 M_2 M_3. \quad (23)$$

264 *5.3. Wave speed estimate*

265 Equation (22) can be rewritten in the more general form:

$$\frac{\partial u}{\partial t} = D\Delta u + bu^n(1-u) - \sigma u. \quad (24)$$

266 Traveling wave solution of (24) satisfies the equation:

$$Dw'' + cw' + bw^n(1-w) - \sigma w = 0. \quad (25)$$

267 Here we will present two analytical methods to approximate the wave speed.

268 *5.3.1. Narrow reaction zone method*

269 One of the methods to estimate the wave speed for the reaction-diffusion
270 equation is the narrow reaction zone method developed in combustion the-
271 ory [34]. Let us rewrite equation (25) in the form:

$$Dw'' + cw' + F(w) - \sigma w = 0, \quad F(w) = w^n(1-w). \quad (26)$$

272 We assume that the reaction takes place at one point $x = 0$ in the coordinates
273 of the moving front. Then, outside of the reaction zone we consider the linear
274 equations:

$$\begin{cases} Dw'' + c_1 w' - \sigma w = 0, & x > 0, \\ Dw'' + c_1 w' = 0, & x < 0. \end{cases} \quad (27)$$

275 These equations should be completed with the jump conditions at the reac-
276 tion zone. In order to derive them, we omit the first derivative w' at the
277 reaction zone since it is small in comparison with two other terms:

$$Dw'' + F(w) = 0. \quad (28)$$

278 Multiplying (28) by w' and integrating through the reaction zone we obtain
279 the following jump conditions:

$$(w'(+0))^2 - (w'(-0))^2 = \frac{2}{D} \int_0^{w^*} F(w) dw, \quad (29)$$

280 considered together with the condition of the continuity of solution $w(+0) =$
281 $w(-0)$.

282 Solving (27) we have:

$$w = \begin{cases} w_*, & x < 0, \\ w_* \exp\left(\frac{-c - \sqrt{c^2 + 4D\sigma}}{2D}\right), & x > 0. \end{cases} \quad (30)$$

283 Then, from (29) and (30) we obtain the following equation for the wave speed:

$$c_1^2 + c_1 \sqrt{c_1^2 + 4D\sigma} + 2D\sigma = A, \quad A = \frac{4D}{w_*^2} \int_0^{w_*} F(w) dw. \quad (31)$$

284 Hence,

$$c_1 = \frac{A - 2D\sigma}{\sqrt{2A}}, \quad A = 4bD \left(\frac{w_*^{n-1}}{n+1} - \frac{w_*^n}{n+2} \right). \quad (32)$$

285 This formula gives a good approximation of the wave speed found numerically
 286 for $n \geq 3$ (Fig. 4). The approximation improves with increasing values of n .
 287 The obtained formula provides an estimation of the speed from below (see
 288 Appendix B for the justification of the method).

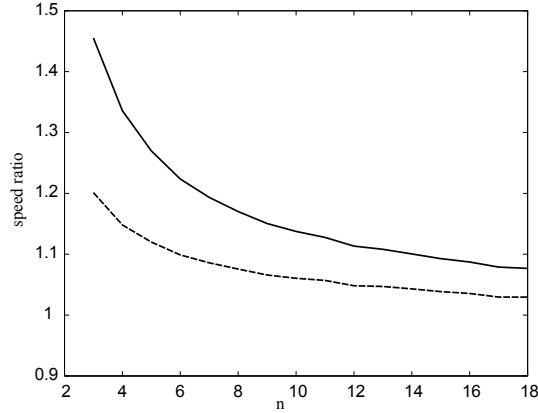


Figure 4: Ratio of wave speeds found numerically and analytically for different values of n ; $\sigma = 0.01$, $D = 2$, $b = 10$. Solid line: $\frac{c}{c_1}$, dashed line $\frac{c}{c_2}$. Parameters of the simulations are provided in Tab. C.1.

289 5.3.2. Piecewise linear approximation

290 Consider equation (26) written in the form

$$Dw'' + cw' + f(w) = 0,$$

291 where $f(w) = w^n(1 - w) - \sigma w$ and $f(0) = f(w_*) = 0$. Let us introduce the
 292 following approximation of this equation:

$$Dw'' + c_2w' + f_0(w) = 0, \quad (33)$$

293 with

$$f_0(w) = \begin{cases} \alpha w, & 0 < w < w_0, \\ \beta(w - w_*), & w_0 < w < w_*, \end{cases} \quad (34)$$

294 where

$$\alpha = f'(0), \quad \beta = f'(w_*). \quad (35)$$

295 In case of equation (24) we have:

$$\alpha = -\sigma, \quad \beta = bnw_*^{n-1} - b(n+1)w_*^n - \sigma. \quad (36)$$

296 We find the value of w_0 from the additional condition:

$$\int_0^{w_*} f(w)dw = \int_0^{w_*} f_0(w)dw. \quad (37)$$

297 Hence we obtain the following equation with respect to w_0 :

$$\frac{\alpha - \beta}{2}w_0^2 + \beta w_* w_0 + r = 0, \quad (38)$$

298 where

$$r = -\beta w_*^2 - \int_0^{w_*} f(w)dw. \quad (39)$$

299 Taking into account the explicit form of function $f(w)$, we obtain:

$$r = bw_*^{n+1} \left(-\frac{n}{2} - \frac{b}{n+1} \right) + bw_*^{n+2} \left(\frac{n+1}{2} + \frac{1}{n+2} \right) + \sigma w_*^2. \quad (40)$$

300 From (38) we get:

$$w_0 = \frac{-\beta w_* + \sqrt{\beta^2 w_*^2 - 2(\alpha - \beta)r}}{\alpha - \beta}. \quad (41)$$

301 Thus, instead of (33) we consider the following equations:

$$\begin{cases} Dw'' + cw' + \beta(w - w_*) = 0, & x < 0, \\ Dw'' + cw' + \alpha w = 0, & x > 0, \end{cases} \quad (42)$$

302 with the additional conditions on the continuity of solution and its first
303 derivative:

$$w(0) = w_0, \quad w'(-0) = w'(+0).$$

304 We find the explicit solution:

$$\begin{cases} w = (w_0 - w_*) \exp\left(x \frac{\sqrt{c_2^2 - 4\beta D} - c_2}{2D}\right) + w_*, & x < 0, \\ w = w_0 \exp\left(x \frac{-\sqrt{c_2^2 - 4\alpha D} - c_2}{2D}\right), & x > 0. \end{cases} \quad (43)$$

305 From the condition of continuity of the derivative we obtain the following
306 formula:

$$c_2 = \frac{\sqrt{D}(\alpha \bar{w}^2 - \beta)}{\sqrt{(\bar{w} - 1)(\alpha \bar{w}^2 - \beta \bar{w})}}, \quad \bar{w} = \frac{w_0}{w_0 - w_*}. \quad (44)$$

307 It gives a good approximation of the wave speed for equation (26) (Fig. 4).

308 *5.4. Comparison of the estimated speed of the wave propagation with the*
309 *complete model and experimental data*

310 *5.4.1. Comparison of the estimated speed with the computational speed in*
311 *system (1)*

312 Considering system (1) and taking the parameter values for (32), (44)
313 according to (23), we approximate the speed of wave propagation by the
314 following formula obtained by the narrow reaction zone method:

$$c_1 = \sqrt{D} \frac{bT_0^2 - \frac{4}{5}bT_0^3 - 2h_2}{\sqrt{2\left(bT_0^2 - \frac{4}{5}bT_0^3\right)}}, \quad (45)$$

315 where

$$b = \frac{k_9 k_{11} \bar{k}_{10} k_8 k_{89} \bar{k}_2 k_5 k_{510} T_0^2}{h_9 h_{10} h_{11} h_8 h_{89} h_5 h_{510}}, \quad (46)$$

316 and by the piecewise linear approximation:

$$c_2 = \frac{\sqrt{D} (-3bT_0^2 - h_2\bar{T} + 4bT_0^3 - h_2)}{\sqrt{(T_0 - 1)\bar{T} (-h_2\bar{T} - 3bT_0^2 + 4bT_0^3 + h_2)}}, \quad (47)$$

317 where:

$$\begin{aligned} \bar{T} &= \frac{T_*}{T_* - T_0}, \quad T_* = \frac{-3bT_0^2 + 4bT_0^4 + h_2}{4bT_0^2 - 3bT_0} + \\ &\frac{\sqrt{(3bT_0^2 - 4bT_0^3 - h_2)^2 - 2b(4T_0 - 3)T_0^2 (-\frac{3}{2}bT_0^2 - \frac{b^2}{4}T_0^2 + \frac{11}{5}bT_0^3 + h_2)}}{4bT_0^2 - 3bT_0}. \end{aligned} \quad (48)$$

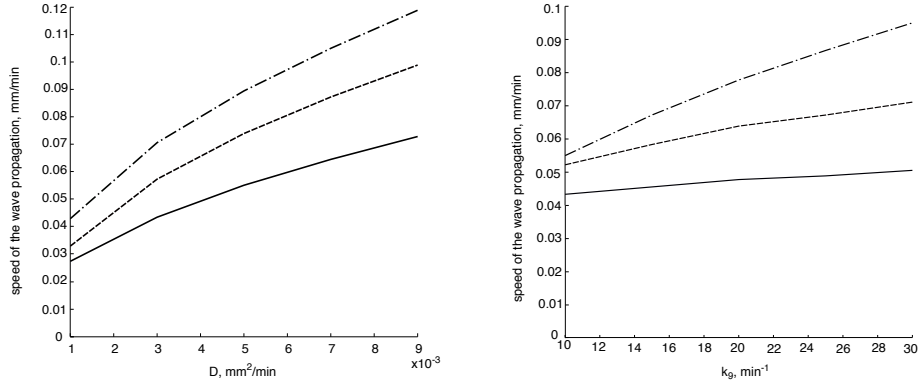


Figure 5: Speeds of wave propagation (mm/min) as function of D (left) and k_9 (right). Solid line: model (1); dashed line: narrow reaction zone approximation; dash-dot line: piecewise linear approximation. Parameters of the simulations are provided in Tab. C.1.

318 We compare the speed of wave propagation for model (1) found numer-
 319 ically with the analytical formulas (Fig. 5). As it was demonstrated above,
 320 the computational speed for the one-equation model is higher than for the
 321 complete model (Fig. 3). The analytical formulas for the speed of the wave
 322 propagation for one-equation model in turn provide the estimates from be-
 323 low (Fig. 4). As the result, the analytical estimates for one equation give
 324 better approximations of the speed in the complete model than the numerical

325 speed for one equation (Fig. 5). If we then compare two different analytical
 326 estimates for the wave speed in one-equation model, we can conclude that
 327 narrow reaction zone method gives the speed further from the one-equation
 328 computational speed than piecewise linear approximation (Fig. 4) but at the
 329 same time it better approximates the wave speed in the complete model (the
 330 narrow reaction zone speed is 1.5 times higher than the computational one).

331 5.4.2. Comparison with experimental data

332 The speed of clot formation has crucial influence on the organism physi-
 333 ology. Coagulation disorders such as hemophilia A, B or C are the result of
 334 severe deficiency of the clotting factors. The effect of this deficiency on the
 335 propagation phase is the most critical for situation *in vivo* [25, 35, 36]. Speed
 336 of the thrombin propagation in mathematical model of the intrinsic pathway
 337 functioning can provide estimation of the clot growth rate dependence on
 338 different factors.

339 As an example, here we consider the experimental results obtained by [25]
 340 on the patients with hemophilia B. Authors examined the effect of factor IX
 341 deficiency on the spatial clotting dynamics. Plasma used was obtained from
 342 hemophiliacs with different extent of the disease and from severe hemophil-
 343 iacs treated with factor IX concentrate (Ahemphil B). Clotting process was
 344 launched through the intrinsic pathway by small artificial contact activation
 345 by plastic material. The obtained results show that the most pronounced
 346 changes in clotting kinetics occurred at factor IX activity less than 20% [25].

347 Experimental data correlate well with the results given by the analytical
 348 estimate of the thrombin propagation speed (Fig. 6). In the lack of precise
 349 kinetic constants we had to fit the approximated speed value at the first point
 350 of the plot corresponding to 1% of factor IX activity. While fitting, we varied
 351 only the value of the parameter b . In terms of our model, factor IX activity is
 352 reflected by the value of the parameter k_9 . Thus, analytical estimate provided
 353 by (45) and (47) are plotted as functions of k_9 and give the values close to
 354 the experimental ones for all the considered range.

355 6. Discussion and conclusions

356 Spatio-temporal dynamics of clot growth is of crucial importance for the
 357 normal organism functioning. The key stage of the blood coagulation pro-
 358 cess determining the dynamics of the clot formation is cumulative thrombin
 359 production due to the intrinsic pathway functioning. Propagating from the

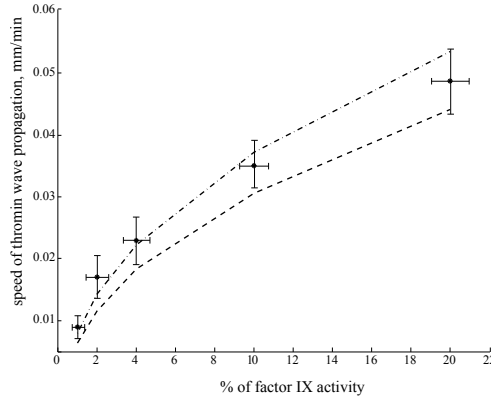


Figure 6: Speeds of the thrombin wave propagation (mm/min) as function of percentage of factor IX activity. Dots: experimental data [25]; dashed line: narrow reaction zone approximation; dash-dot line: piecewise linear approximation (Tab. 1)

injury site with constant velocity during the amplification phase, thrombin concentration can be modeled as traveling wave solutions in the PDE system on plasma factor concentrations [26]. In the current work we derive conditions on the existence and stability of the traveling wave solutions for the system describing intrinsic pathway of blood coagulation cascade.

Despite the general character of the methods used in this work, the developed approaches imply some limitations. In our model we considered only a part of the coagulation cascade (intrinsic pathway) without taking into account neither the initial activation, nor the role of the activated protein C pathway. In terms of our model, initial thrombin formation appears on the left boundary of the domain. However, since the problem of the existence of the traveling wave solutions is considered on the whole axis, the solutions do not depend on the boundary conditions. The independence of the speed of the thrombin wave propagation during the amplification phase on the nature of the stimuli that launched the clotting process was also demonstrated in multiple experimental studies [2, 11, 25]. Then, inhibition role of the activated protein C appears only in the proximity of the vessel wall due to its activation by thrombomodulin and thus does not directly impact thrombin propagation on the distance from the vessel wall [37] and we do not incorporate it in our model. As the result, considered model is monotone, that is equivalent to positive contribution of all factors to the activation reactions in terms of the chemical reaction network. This important feature of the coagulation cascade model allows us to study existence and properties of its

383 wave solutions.

384 The most important parameter determining the dynamics of clot growth
 385 is the speed of the thrombin wave propagation or, in terms of the mathemat-
 386 ical model, the speed of propagation of the reaction-diffusion wave. In the
 387 current work we obtain analytical formula for the speed of wave propagation
 388 in the model of blood coagulation. We reduce the system of equations to
 389 one equation on the thrombin concentration and then determine the wave
 390 speed for this equation. The method of reduction is based on the minimax
 391 representation of the wave speed applicable for monotone reaction-diffusion
 392 systems. One-equation model gives the speed of the wave propagation above
 393 the wave speed obtained in the initial system. The difference dues to the as-
 394 sumption on the fast reactions applied for the derivation of the one-equation
 395 model. Analytical estimates obtained for the wave speed in one-equation
 396 model in turn provide its approximation from below. Since narrow reaction
 397 zone method was originally developed for the description of the flame front
 398 propagation in the combustion theory with the exponential function in reac-
 399 tion term. In our work thrombin activation is described with the polynomial
 400 of the third degree that makes the obtained estimate less precise. Never-
 401 theless, the obtained analytical estimates give good approximation of both
 402 computational and experimental speed of the thrombin propagation.

403 The described approach for system analysis and estimation of the wave
 404 propagation speed can be further expanded on other cascade models. An-
 405 alytical formulas for the reaction front propagation can provide important
 406 information on the system response on different factors and is of big impor-
 407 tance for the model validation.

408 **Appendix A. Proof of the Theorem 1**

409 *Proof.* Along with the system system

$$\frac{du}{dt} = F(u), \quad (\text{A.1})$$

410 consider the system

$$\frac{du}{dt} = F_{\tau}(u), \quad (\text{A.2})$$

411 which depends on the parameter $\tau \in [0, 1]$. They differ only by the equation
 412 for T which is considered now in the following form:

$$\frac{dT}{dt} = (\tau U_{10} + (1 - \tau)\varphi_{10}(T)) \left(k_2 + \overline{k_2} \frac{k_{510}}{h_{510}} (\tau U_5 + (1 - \tau)\varphi_5(T)) \right) \left(1 - \frac{T}{T_0} \right) - h_2 T.$$

413 Here the functions $\varphi_i(T)$ are determined by the equalities:

$$\begin{aligned} \varphi_{11}(T) &= \frac{k_{11}}{h_{11}} T, \quad \varphi_9(T) = \frac{k_9 k_{11}}{h_9 h_{11}} T, \quad \varphi_5(T) = \frac{k_5}{h_5} T, \quad \varphi_8(T) = \frac{k_8}{h_8} T, \\ \varphi_{10}(T) &= \frac{k_9 k_{11}}{h_{10} h_9 h_{11}} \left(k_{10} T + \overline{k_{10}} \frac{k_{89}}{h_{89}} T^2 \right). \end{aligned}$$

414 We can express U_i , $i = 5, 8, 9, 10, 11$ as functions of T from the corresponding
415 equations in (A.1) or, the same, from (A.2): $U_i = \varphi_i(T)$. Therefore the
416 solutions of the system of equations $F_\tau(T) = 0$ coincide with the solutions of
417 the system $F(T) = 0$.

418 Thus, systems (A.1) and (A.2) have the same stationary solutions for all
419 $\tau \in [0, 1]$. For $\tau = 1$ these two systems coincide. For $\tau = 0$ the equation
420 for T in (A.2) does not depend on other variables. This will allow us to
421 determined the eigenvalues of the corresponding linearized matrix.

422 It can be verified by the direct calculations that $\det F'_\tau(u^*) = 0$ if and
423 only if $\det F'(u^*) = 0$ for all $\tau \in [0, 1]$. Suppose that the latter is different
424 from zero. Then the principal eigenvalue of the matrix F'_τ , which is real and
425 simple, cannot change sign when τ changes from 0 to 1. Hence the sign of
426 the principal eigenvalue of the matrix $F'(u^*)$ is the same as for the matrix
427 $F'_0(u^*)$. This matrix has the form:

$$F'_0(u^*) = \begin{matrix} & T & U_5 & U_8 & U_{11} & U_9 & U_{10} \\ \begin{matrix} T \\ U_5 \\ U_8 \\ U_{11} \\ U_9 \\ U_{10} \end{matrix} & \begin{pmatrix} -P'(T^*) & 0 & 0 & 0 & 0 & 0 \\ k_5 & -h_5 & 0 & 0 & 0 & 0 \\ k_8 & 0 & -h_8 & 0 & 0 & 0 \\ k_{11} & 0 & 0 & -h_{11} & 0 & 0 \\ 0 & 0 & 0 & k_9 & -h_9 & 0 \\ 0 & 0 & \overline{k_{10}} \frac{k_{89}}{h_{89}} U_9^* & 0 & k_{10} + \overline{k_{10}} \frac{k_{89}}{h_{89}} U_8^* & -h_{10} \end{pmatrix} \end{matrix}$$

428 The principal eigenvalue of this matrix is positive if $P'(T^*) < 0$ and negative
429 if this inequality is opposite.

430 □

431 Appendix B. Justification of the narrow reaction zone method

432 Consider equation (26) and suppose for simplicity that $F(u) = 0$ for
 433 $u \leq u_0$ and $F(u) > 0$ for $u_0 < u < 1$. Let u^* be the maximal solution of the
 434 equation $F(u) = \sigma u$ (Figure B.7). We will look for a decreasing solution of
 435 equation (26) with the limits:

$$u(-\infty) = u^*, \quad u(+\infty) = 0.$$

436 Multiplying the equation (26) by u' and integrate through the hole axis we
 437 obtain:

$$c = \frac{\int_0^{u^*} F(u) du - \frac{1}{2} \sigma (u^*)^2}{\int_{-\infty}^{\infty} (u'(x))^2 dx}. \quad (\text{B.1})$$

438 Along with equation (26) we consider the system of two first-order equations:

$$\begin{cases} u' = p, \\ p' = -cp - F(u) + \sigma u. \end{cases} \quad (\text{B.2})$$

439 The wave solution of (26) corresponds to the trajectory connecting the sta-
 440 tionary points $(u^*, 0)$ and $(0, 0)$ (Figure B.7). This trajectory coincides with
 441 the line $p = \lambda u$ for $0 < u \leq u_0$, where λ is a negative solution of the equation

$$\lambda^2 + c\lambda - \sigma = 0.$$

442 The integral in the denominator of (B.1) can be approximated by replacing
 443 the trajectory function by the straight line $p = -\lambda u$:

$$\int_{-\infty}^{\infty} (u'(x))^2 dx = \int_0^{u^*} p(u) du \approx \frac{1}{2} \lambda (u^*)^2.$$

444 Substituting this expression into (B.1) we obtain the same formula for the
 445 speed as by the narrow reaction zone method (32).

446 Thus, narrow reaction zone method is equivalent to replacing the equa-
 447 tion trajectory by the straight line. Hence we can conclude that this method
 448 provides the estimate of the speed from below, and it also gives asymptoti-
 449 cally correct result in the limiting case as the support of the function $F(u)$
 450 converges to a point.

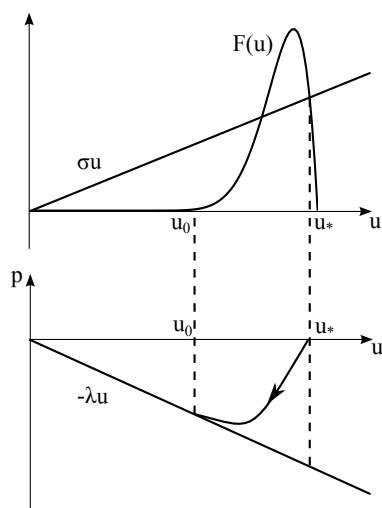


Figure B.7: Illustration of the narrow reaction zone method approximation.

451 Appendix C. Parameter values used for the simulations

Table C.1: Parameter rates used for the modeling of the coagulation cascade.

parameter	value	units	reference
k_{11}	0.000011	min^{-1}	[12]
h_{11}	0.5	min^{-1}	[38]
k_{10}	0.00033	min^{-1}	[39]
\overline{k}_{10}	500	min^{-1}	[39]
h_{10}	1	min^{-1}	[40]
k_9	20	min^{-1}	[41]
h_9	0.2	min^{-1}	[42]
k_{89}	100	$\text{nM}^{-1}\text{min}^{-1}$	[30]
h_{89}	100	min^{-1}	[30]
k_8	0.00001	min^{-1}	[30]
h_8	0.31	min^{-1}	[43]
k_5	0.17	min^{-1}	[30]
h_5	0.31	min^{-1}	[30]
k_{510}	100	$\text{nM}^{-1}\text{min}^{-1}$	[30]
h_{510}	100	min^{-1}	[30]
k_2	2.45	min^{-1}	[44]
\overline{k}_2	2000	min^{-1}	[44]
h_2	1.45	min^{-1}	[33]
K_{2m}	58	nM	[44]
\overline{K}_{2m}	210	nM	[44]
D	0.0037	$\text{mm}^2\text{min}^{-1}$	[30]
T_0	1400	nM	[1]

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